

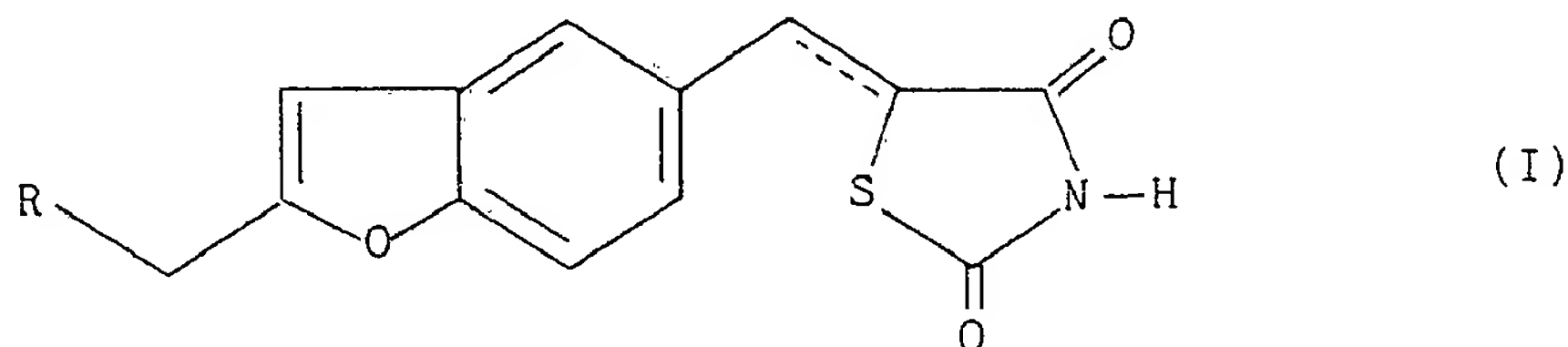


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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 654899

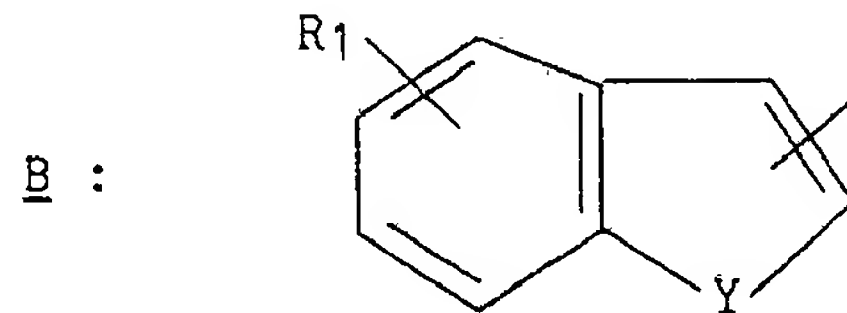
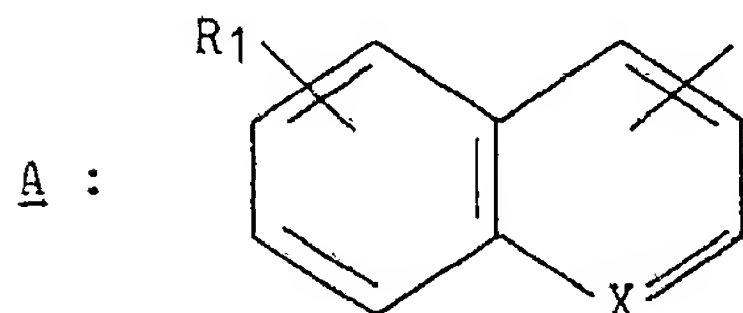
- (54) Title
NEW 2,4-THIAZOLIDINEDIONE COMPOUNDS, PROCESS FOR PREPARING THEM AND
PHARMACEUTICAL COMPOSITIOS CONTAINING THEM
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- (57) Claim

1. A compound of formula (I):



in which:

- the broken line denotes the presence or absence of a double bond,
- R represents one of the following groups A or B:



in which:

- R₁ represents a hydrogen or halogen atom, a linear or branched (C₁-C₆) alkyl group or a linear or branched (C₁-C₆) alkoxy group,

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- X represents a CH radical or a nitrogen atom,
- Y represents an NH radical or an oxygen or sulfur atom, and its isomers, enantiomers and epimers as well as its addition salts with a pharmaceutically acceptable acid.

6. The pharmaceutical composition as claimed in claim 5, containing at least one active principle as claimed in any one of claims 1 to 3, which is useful in the treatment of non-insulinopenic diabetes, associated with hypertension or otherwise.

AUSTRALIA

Patents Act 1990

654899

**ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT**

Application Number:

Lodged:

Invention Title:

NEW 2,4-THIAZOLIDINEDIONE COMPOUNDS, PROCESS FOR
PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM.

The following statement is a full description of this invention, including the
best method of performing it known to :-US

The present invention relates to new 2,4-thiazolidinedione compounds, to a process for preparing them and to pharmaceutical compositions containing them.

Many 2,4-thiazolidinedione compounds are already described in the prior art as antidiabetic agents, for example in Patents EP-A-356,214 or WO-A-86/07056.

Patent EP-A-299,620 mentions benzofuranylmethyl- 2,4-thiazolidinedione compounds substituted with phenyl or substituted phenyl, pyridyl or substituted pyridyl and oxazolyl or substituted oxazolyl groups.

In Patent WO-A-91/12003, a description is given of thiazolidinedione compounds which are known as antidiabetic agents and used for their antihypertensive property in insulin-resistant subjects.

The compounds of the present invention, apart from being new, differ from the other 2,4-thiazolidinedione compounds in the intensity of their pharmacological properties.

In effect, insulin resistance and deficiency in insulin secretion are the factors responsible for the glucose intolerance observed in patients having non- insulin-dependent diabetes.

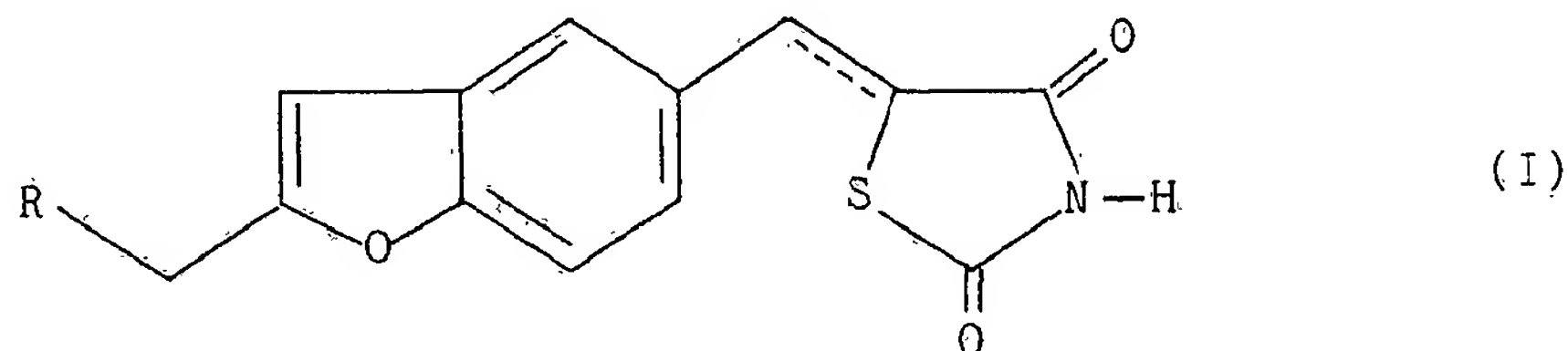
The therapies currently available enable the deficiency in insulin secretion to be substantially corrected without necessarily improving the sensitivity of the peripheral tissues (muscles, adipose tissue) to insulin.

Compounds belonging to the 2,4-thiazolidinedione structure are capable of causing a drop in blood sugar level and of improving glucose tolerance in models of non-insulin-dependent diabetes without causing an increase in insulin secretion. Our compounds possess the advantage of being especially potent, more particularly in comparison to ciglitazone, a reference compound belonging to this chemical structure and whose efficacy remains low.

Thus, the compounds of the invention may be used in the treatment of non-insulinopenic diabetic states, enabling better control of the blood sugar level to be obtained while the circulating insulin level decreases. Prevention of this relative hyperinsulinemia, associated with a decrease in

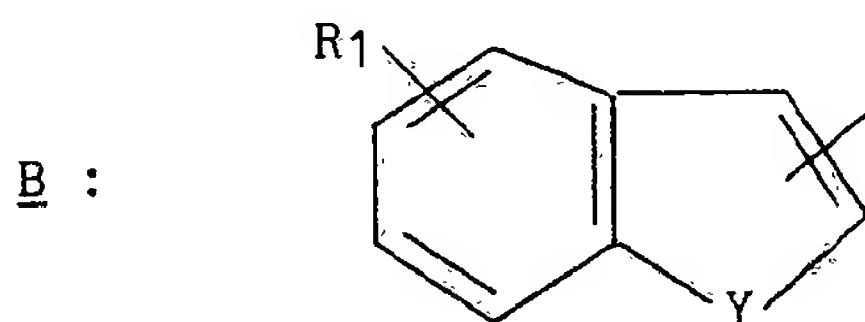
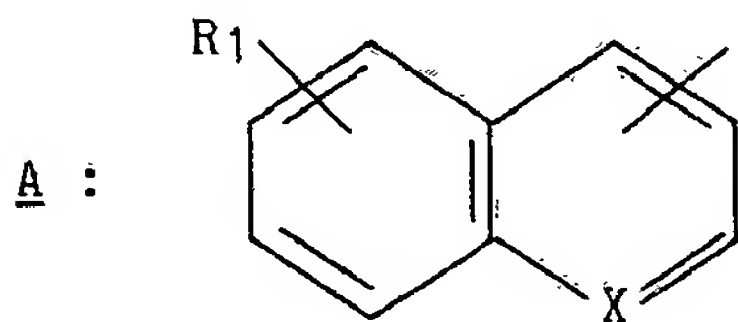
circulating triglycerides through the effect of these products, may contribute to a reduction in the risks of macroangiopathy.

These same compounds find a use, furthermore, in the treatment of hypertension in subjects exhibiting an insulin resistance, associated with other metabolic abnormalities or otherwise. More specifically, the present invention relates to the compounds of formula (I):



in which:

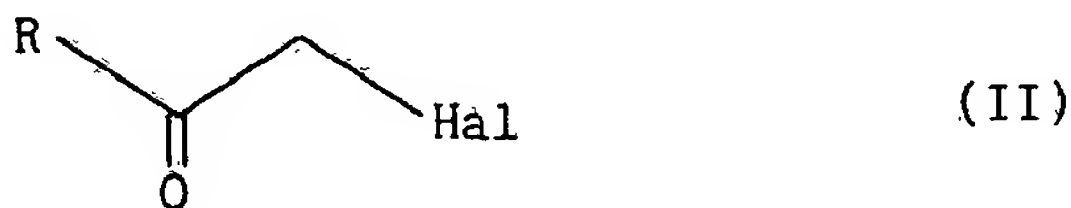
- the broken line denotes the presence or absence of a double bond,
- R represents one of the following groups A or B:



in which:

- R₁ represents a hydrogen or halogen atom, a linear or branched (C₁-C₆) alkyl group or a linear or branched (C₁-C₆) alkoxy group,
 - X represents a CH radical or a nitrogen atom,
 - Y represents an NH radical or an oxygen or sulfur atom,
- and their isomers, enantiomers and epimers as well as their addition salts with a pharmaceutically acceptable acid.

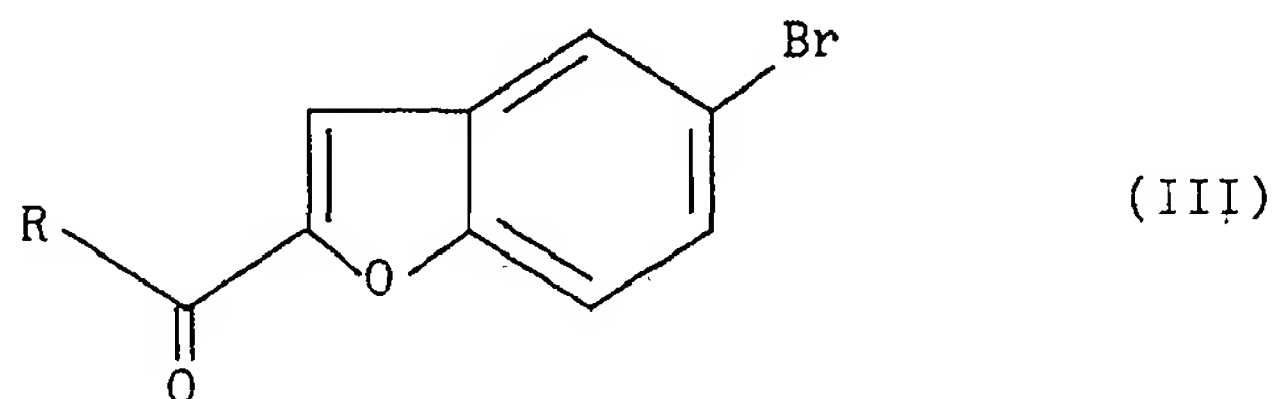
The invention also encompasses the process for preparing the compounds of formula (I), wherein a compound of formula (II):



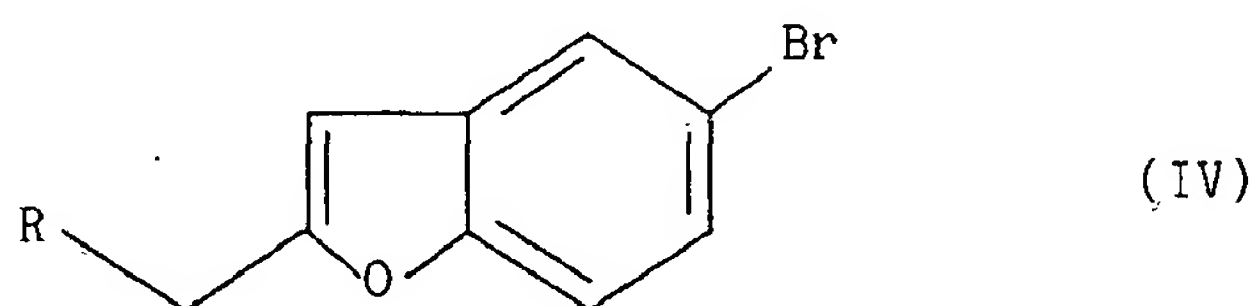
in which:

- R is defined as in the formula (I),

- Hal represents a chlorine or bromine atom,
is reacted with 5-bromosalicylaldehyde in the presence of an
alkali metal salt, for example potassium carbonate, to give
(III):

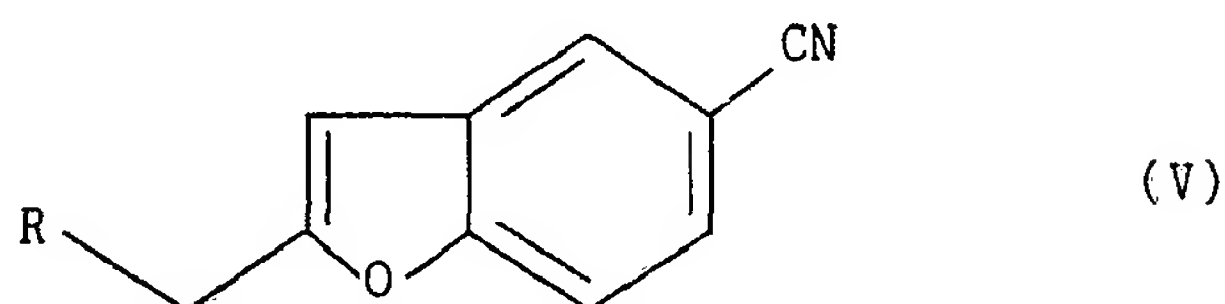


where R is as described in (II), which, when subjected to the
action of triethylsilane, is reduced to (IV):

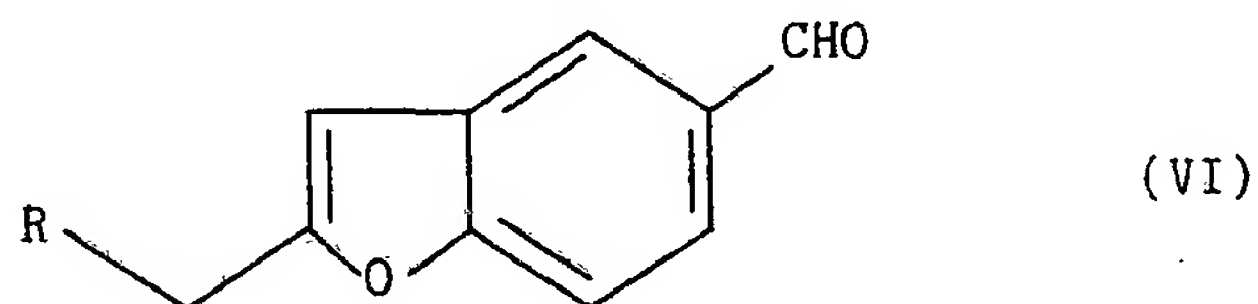


in which formula R is as described above,

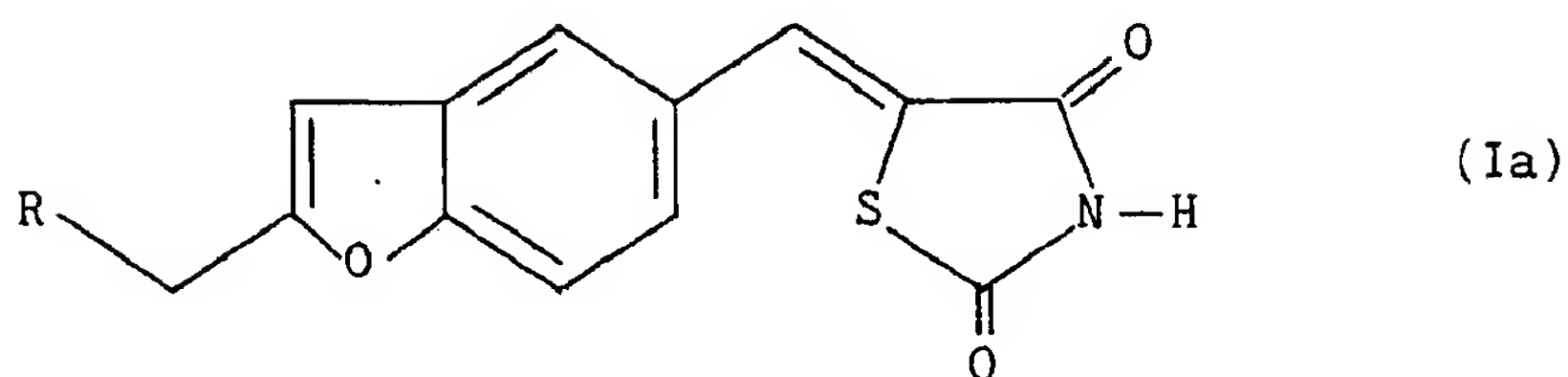
10 which is converted to a compound of formula (V) with cuprous
cyanide:



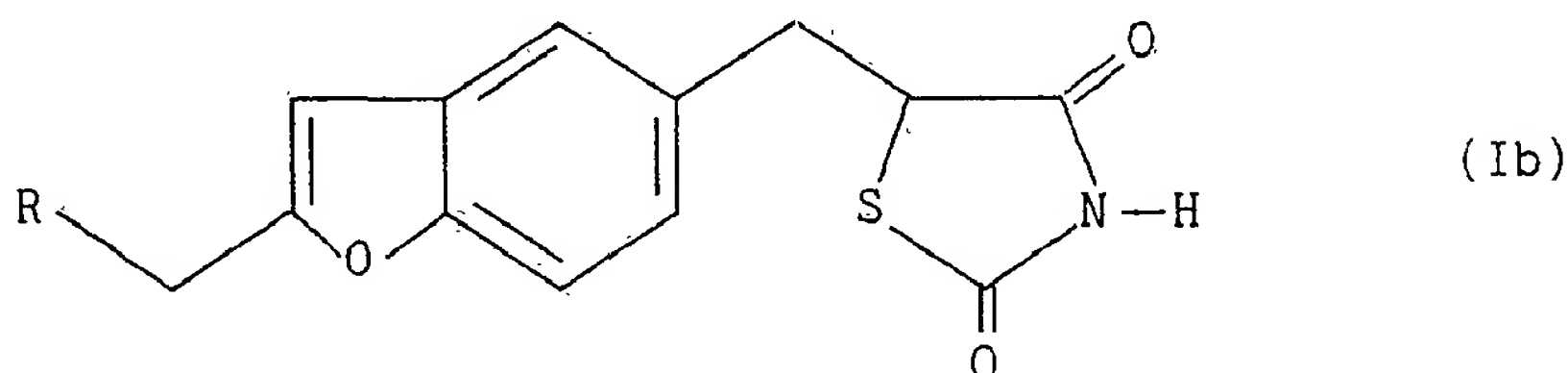
15 where R is as described above, to give, by reaction with an
aluminum/nickel amalgam in the presence of acid such as, for
example, trifluoroacetic acid, the compound of formula (VI),
these last two steps being described by R.L. Dow et al. (J.
Med. Chem., 34, (1988), 1538-1544):



20 in which R has the same meaning as above, which compound (VI)
is condensed with 2,4-thiazolidinedione in the presence of a
base such as piperidine so as to obtain the compound (Ia), a
special case of the compounds of formula (I):



where R is as described above, which, on catalytic hydrogenation, yields the product (Ib), a special case of the compounds of the formula (I):



where R is as described above,
which compounds of formulae (Ia) and (Ib) are purified, where appropriate, according to a standard purification technique, and the isomers of which are separated, if so desired, by a standard separation technique, and which are converted, if necessary, to their addition salts with a pharmaceutically acceptable acid.

The compounds of formula (I) possess very advantageous pharmacological properties. In effect, thiazolidinedione compounds are generally inactive in vitro and in normoglycemic animals not exhibiting an abnormality of glucose tolerance. The pharmacological study of the compounds of the invention is hence carried out:

- in a model of non-insulin-dependent diabetes (NIDDM): the ob/ob mouse, and
- in a model of decreased glucose tolerance associated with hyperinsulinemia and hyperlipidemia: the Zucker FaFa rat.

The results obtained in these tests show that the compounds of the invention permit control of the blood sugar level while the triglyceride and circulating insulin levels decrease.

In addition to these pharmacological properties relating to hyperinsulinemia, the compounds of formula (I), though devoid of intrinsic hypotensive activity, decrease arterial blood pressure in insulin-resistant subjects and, as a result, may

be used in therapy in the treatment of hypertension associated with insulin-resistance states and of other metabolic disorders such as, for example, obesity, dyslipidemia, hyperinsulinemia, and the like, which constitute considerable cardiovascular risk factors (coronary disease, macroangiopathy, and the like).

The subject of the present invention is also pharmaceutical compositions containing as active principle at least one compound of formula (I) or one of its physiological tolerable salts, alone or in combination with one or more pharmaceutically suitable excipients.

The pharmaceutical compositions of the invention thereby obtained are advantageously presented in forms suitable for oral, parenteral or nasal administration, such as, for example, tablets (simple or sugar-coated), sublingual tablets, hard gelatin capsules, troches, as well as in the form of suppositories, creams, ointments, skin gels, and the like.

The appropriate dosage varies according to the patient's age and weight, the nature and severity of the disorder and the administration route, and according to the nature of associated treatments. Generally speaking, the dosage ranges from 50 to 1000 mg of active principle of the invention, taken in 1 to 3 doses per 24 hours.

The examples which follow illustrate the present invention without, however, limiting it in any way. The starting materials are known, or are prepared according to standard procedures from known starting materials.

EXAMPLE 1 : 5-[2-(2-Naphthylmethyl)-5-benzofuranyl-methylene]-2,4-thiazolidinedione

First step : 2-(2-Naphthoyl)-5-bromobenzofuran

186 g (0.74 mol) of 2-bromo-2'-acetoneaphthone, 150 g (0.74 mol) of 5-bromosalicylaldehyde and 103 g (0.74 mol) of potassium carbonate are mixed in 3.5 liters of methyl cyanide; the mixture is then brought to reflux overnight. The mixture

is cooled to 0°C and then filtered to give 220 g of a brown solid, which is washed and dried.

Melting point : 158-159°C

Second step : 2-(2-Naphthylmethyl)-5-bromobenzofuran

5 220 g (0.63 mol) of product obtained above are added to 1.5 liters of trifluoroacetic acid and the mixture is cooled to 0°C. 220 ml (1.38 mol) of triethylsilane are added dropwise and the temperature is maintained for 2 hours at 0°C. After evaporation of the trifluoroacetic acid, the residue is
10 taken up with ethyl acetate, and the organic phase is washed with water and then with saturated sodium chloride solution before being dried over magnesium sulfate. After evaporation
of the solvent and purification on a silica column (eluant: cyclohexane/methylene chloride, 95:5), 75 g of expected
15 product are obtained.

Melting point : 98-100°C

Third step : 2-(2-Naphthylmethyl)-5-cyanobenzofuran

75 g (0.22 mol) of product obtained in the second step are
added at room temperature to 40 g (0.44 mol) of cuprous
20 cyanide in 620 ml of dimethylformamide. The mixture is brought to 150°C for 48 hours; 20 g (0.22 mol) of cuprous cyanide are
then added, and the mixture is again brought to 150°C for 60
hours.

When it has returned to room temperature, the reaction mixture
25 is poured into 300 ml of concentrated ammonia solution, producing a blue coloration. After extraction with ethyl acetate, drying over magnesium sulfate and evaporation of the solvents, 60 g of a black oil are obtained. Purification on a
silica column gives the expected product in the form of a
30 white solid.

Melting point : 202-203°C

Fourth step : 2-(2-Naphthylmethyl)-5-formylbenzofuran

21 g (74.2 mmol) of the product of the third step are introduced at room temperature into a round-bottomed flask containing 22.3 g of an aluminum/nickel amalgam in 220 ml of 70 % formic acid. The mixture is brought to reflux for 2 hours 30 minutes. After returning to room temperature, the reaction mixture is filtered and the solid residues are washed with 70 % formic acid.

The filtrate is extracted with ethyl acetate and the Ni/Al amalgam taken up several times with boiling ethyl acetate. The organic phases are washed with 4N sodium hydroxide solution until the pH reaches a constant value of 12. After washing with water, these organic phases are dried and evaporated to obtain 19.7 g of the expected product.

Melting point : 97-101°C

Fifth step : 5-[2-(2-Naphthylmethyl)-5-benzofuranylmethylene]-2,4-thiazolidinedione

19.7 g (68.8 mmol) of the aldehyde obtained in the fourth step is brought into contact at room temperature with 8.1 g (69.2 mmol) of 2,4-thiazolidinedione and 5 ml of piperidine in 650 ml of absolute ethanol. The mixture is brought to reflux overnight and then cooled to room temperature. The solvent is evaporated off and a thick oil is obtained. The latter is taken up with isopropanol, in which the oil precipitates. The solid obtained (7.3 g) is filtered off and then dried.

Melting point : 210°C

EXAMPLE 2 : 5-[2-(2-Naphthylmethyl)-5-benzofuranylmethyl]-2,4-thiazolidinedione

5.5 g (14.3 mmol) of compound obtained in Example 1 are introduced into an autoclave at room temperature with 5 g of

palladium (in a 10 % dispersion in charcoal) in 80 ml of tetrahydrofuran. The autoclave is pressurized to 60 kg and reaction is performed at 60°C for 2 days. After purification on a silica column and evaporation of the solvents, the solid is washed with ether, and 530 mg of white product are obtained.

Melting point : 151-153°C

Elementary microanalysis :

	C %	H %	N %	S %
10 calculated	71.30	4.42	3.61	8.28
found	71.12	4.43	3.95	8.15

EXAMPLE 3 : 5-[2-(2-Quinolylmethyl)-5-benzofuranylmethylene]-2,4-thiazolidinedione

The product is prepared according to the same procedure as that described for Example 1, the first step in this case being a reaction between 5-bromosalicylaldehyde and bromomethyl 2-quinolyl ketone.

EXAMPLE 4 : 5-[2-(2-Benzofuranylmethyl)-5-benzofuranylmethylene]-2,4-thiazolidinedione

This compound is prepared according to the procedure in Example 1, using bromomethyl 2-benzofuranyl ketone as starting material.

EXAMPLE 5 : 5-[2-(-Indolylmethyl)-5-benzofuranylmethylene]-2,4-thiazolidinedione

Preparation process identical to that of Example 1, using bromomethyl 2-indolyl ketone as starting material.

EXAMPLE 6 : 5-[2-(2-Benzo[b]thienylmethyl)-5-benzofuranylmethylene]-2,4-thiazolidinedione

This compound is prepared according to the procedure of Example 1, using bromomethyl 2-benzo[b]thienyl ketone as starting material.

5 EXAMPLE 7 : 5-[2-(1-Naphthylmethyl)-5-benzofuranylmethylene]-2,4-thiazolidinedione

Preparation process identical to that of Example 1, the starting material being bromomethyl-1-naphthyl ketone.

10 Examples 8 to 12 below afford the hydrogenated products of the compounds of Examples 3 to 7 respectively. The hydrogenations are performed according to the procedure described in Example 2.

11 EXAMPLE 8 : 5-[2-(2-Quinolylmethyl)-5-benzofuranylmethyl]-2,4-thiazolidinedione

Obtained by hydrogenation of the compound of Example 3.

15 EXAMPLE 9 : 5-[2-(2-Benzofuranylmethyl)-5-benzofuranylmethyl]-2,4-thiazolidinedione

Obtained by hydrogenation of the compound of Example 4.

16 EXAMPLE 10 : 5-[2-(2-Indolylmethyl)-5-benzofuranylmethyl]-2,4-thiazolidinedione

20 Obtained by hydrogenation of the compound of Example 5.

21 EXAMPLE 11 : 5-[2-(2-Benzo[b]thienylmethyl)-5-benzofuranylmethyl]-2,4-thiazolidinedione

Obtained by hydrogenation of the compound of Example 6.

25 EXAMPLE 12 : 5-[2-(1-Naphthylmethyl)-5-benzofuranylmethyl]-2,4-thiazolidinedione

Obtained by hydrogenation of the compound of Example 7.

EXAMPLES 13 AND 14 : Enantiomers of example 2

EXAMPLE 13 : 5-[2-(2-Naphtylmethyl)-5-benzofuranylmethyl]-
2,4-thiazolidinedione, isomer α

5 EXAMPLE 14 : 5-[2-(2-Naphtylmethyl)-5-benzofuranylmethyl]-
2,4-thiazolidinedione, isomer β

Isomers α and β of compound of example 2 have been separated
by chiral chromatography under following conditions :

Column : stainless steel, L = 25 cm,

10 internal diameter : 4 mm

Stationary phase : Chiralcel OJ (DIACEL)

Mobil phase : Ethanol/hexane (5/5)

Temperature : 35°C

Flow rate : 0.9 ml/min

15 Detection : UV - 254 nm

Retention time : isomer α : 35 min

isomer β : 62 min

PHARMACOLOGICAL STUDY

20 EXAMPLE 15 : Study of the activity of the compounds of the
invention on a model of non-insulin- dependent
diabetes (NIDDM)

The animals (ob/ob mice) are treated every day for 4 days by
oral administration of the compounds of the invention
suspended in a 20 % solution of gum arabic.

25 Before and after treatment, that is to say at D₀ and at D₅,
the blood is sampled by puncture of the orbital sinus and the
blood sugar level is determined.

Table 1 shows the doses of the different products to be
administered in order to obtain the same hypoglycemic effect
30 (base value 100).

- Table 1 : Doses producing the same hypoglycemic effect in ob/ob mice -

	Pioglitazone	Englitazone	CS 045	Ciglitazone	Example 2
Dose (mg/kg/day) for 4 days	10	10-20	150-200	50-100	5-10
Hypoglycemic power	100	100	100	100	100

5 The study of a dose effect shows that the dose giving a 30 % decrease in the initial blood sugar level, ED₃₀, for the compound of Example 2 is less than 0.1 mg/kg, whereas that for pioglitazone is between 5 and 10 mg/kg. The minimum active dose, MAD, showing a 10 to 15 % decrease in the blood sugar level is 0.1 mg/kg for the compound of Example 2, whereas it is 3 mg/kg for pioglitazone.

EXAMPLE 16 : Study of the activity of the compounds of the invention on a model of decreased glucose tolerance associated with hyperinsulinemia and hyperlipidemia

15 The animals (male Zucker Fa/Fa rats) are treated every day for 10 days by oral administration of the compounds of the invention, at a dose of 5 mg/kg/day, suspended in a 20 % solution of gum arabic. On the 11th day, the animals are sacrificed and the blood is collected in order to determine the blood sugar, plasma triglyceride and immunoreactive insulin levels. The animals are, moreover, weighed before and after treatment.

20 Under these conditions, the compounds of the invention have no influence on the circulating glucose level, but decrease the level of plasma triglycerides and free fatty acids as well as that of immunoreactive insulin. This activity is equal to or greater than that of other, reference thiazolidinedione compounds.

- Table 2 : Pharmacological study on male Zucker Fa/Fa rats -

	Dose (mg/kg/day) for 10 days	Weight Δ W % D ₁₁ -D ₁ ^o	Blood sugar level (%)	Plasma insulin (%)	TG (%)	FFA (%)
Control	0	100	100	100	100	100
Pioglitazone	5	219	103	61	44	52
Example 2	5	250	97	50	35	48

(TG = triglycerides ; FFA = free fatty acids)

PHARMACEUTICAL COMPOSITION

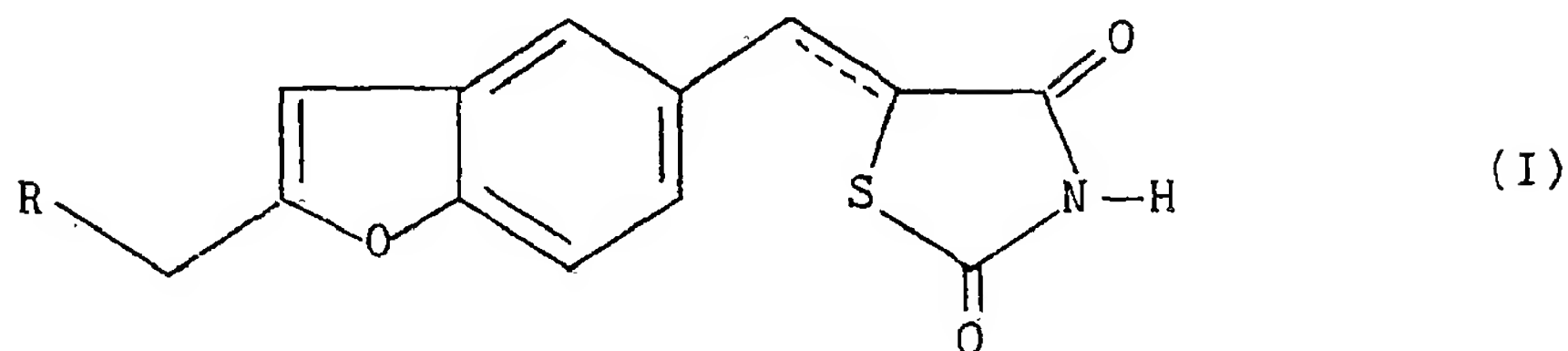
EXAMPLE 17 : Tablet : Preparation formula for 1000
tablets containing a 50 mg dose

5-[2-(2-Naphthylmethyl)-5-benzofuranylmethyl]-
2,4-thiazolidinedione 50 g
Hydroxypropylcellulose 2 g
Wheat starch 10 g
Lactose 100 g
Magnesium stearate 3 g
Talc 3 g

CLAIMS

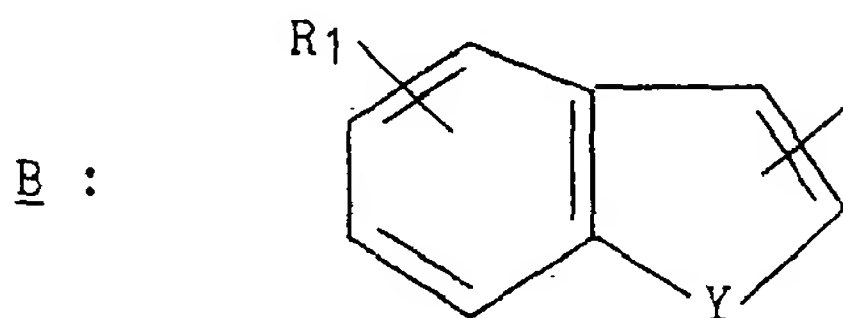
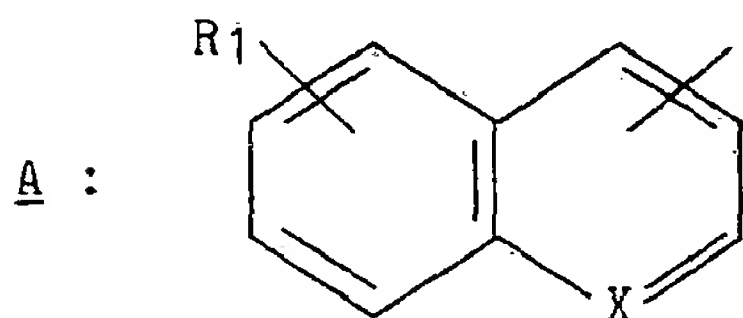
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula (I):



in which:

- the broken line denotes the presence or absence of a double bond,
- R represents one of the following groups A or B:



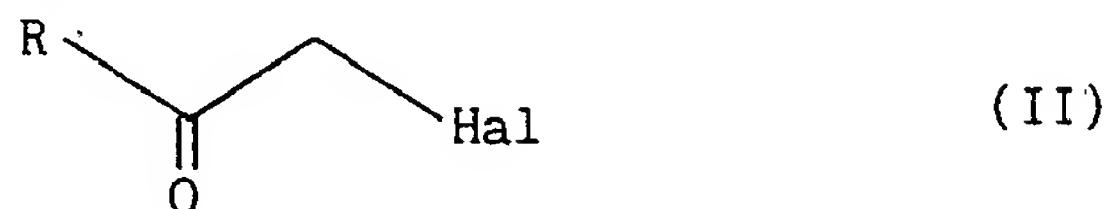
in which:

- R₁ represents a hydrogen or halogen atom, a linear or branched (C₁-C₆) alkyl group or a linear or branched (C₁-C₆) alkoxy group,
 - X represents a CH radical or a nitrogen atom,
 - Y represents an NH radical or an oxygen or sulfur atom,
- and its isomers, enantiomers and epimers as well as its addition salts with a pharmaceutically acceptable acid.

2. A compound of formula (I) as claimed in claim 1, in which the group R represents a naphthyl radical, its isomers, enantiomers and epimers as well as its addition salts with a pharmaceutically acceptable acid.

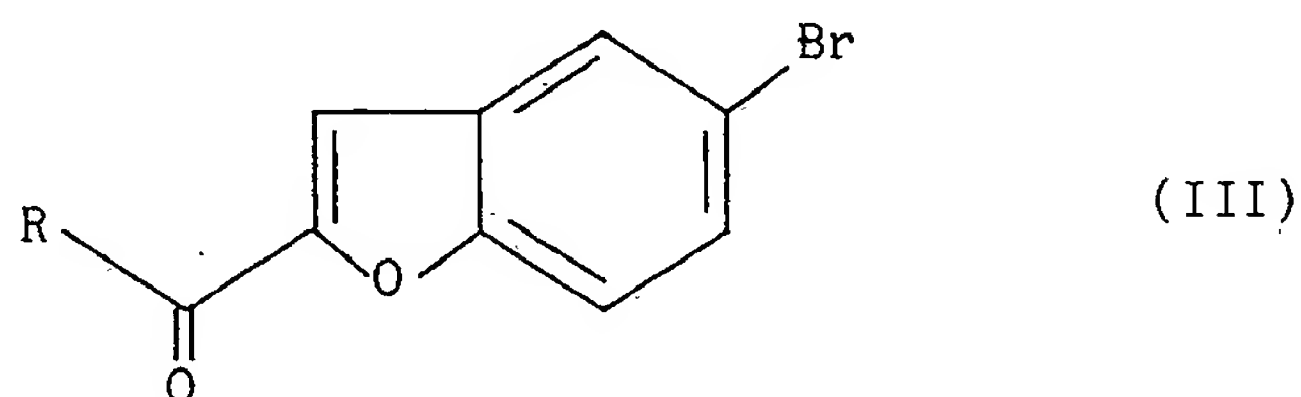
3. The compound of formula (I) as claimed in claim 1, which is 5-[2-(2-naphthylmethyl)-5-benzofuranylmethyl]-2,4-thiazolidinedione, its enantiomers and epimers as well as its addition salts with a pharmaceutically acceptable acid.

4. A process for preparing a compound of formula (I), wherein a compound of formula (II):

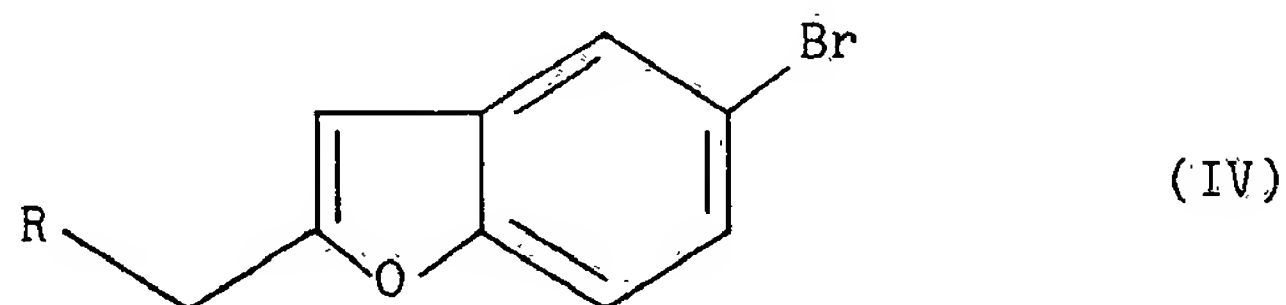


in which:

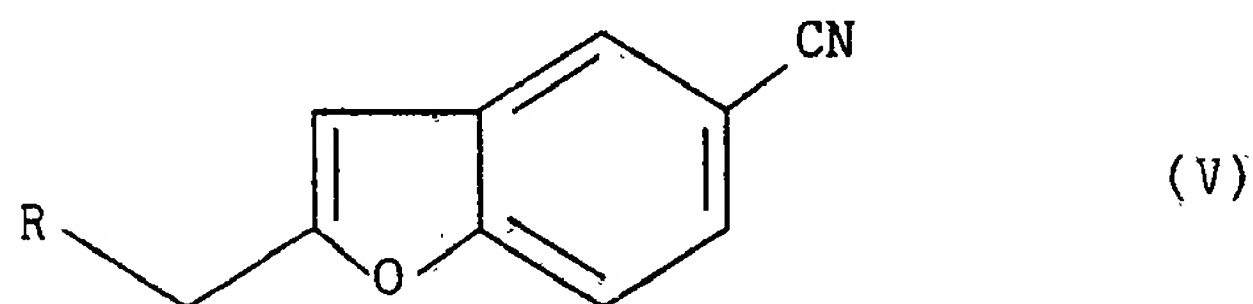
- R is defined as in the formula (I),
 - Hal represents a chlorine or bromine atom,
- is reacted with 5-bromosalicylaldehyde in the presence of an alkali metal salt, for example potassium carbonate, to give (III):



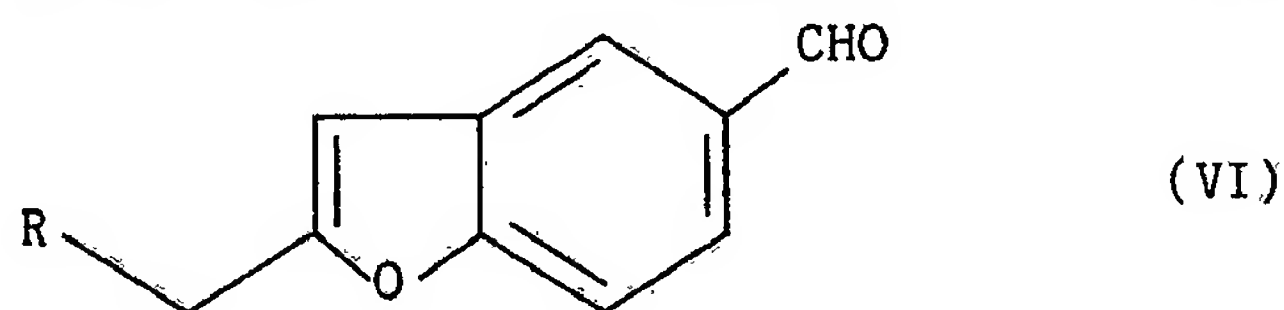
where R is as described in (II), which, when subjected to the action of triethylsilane, is reduced to (IV):



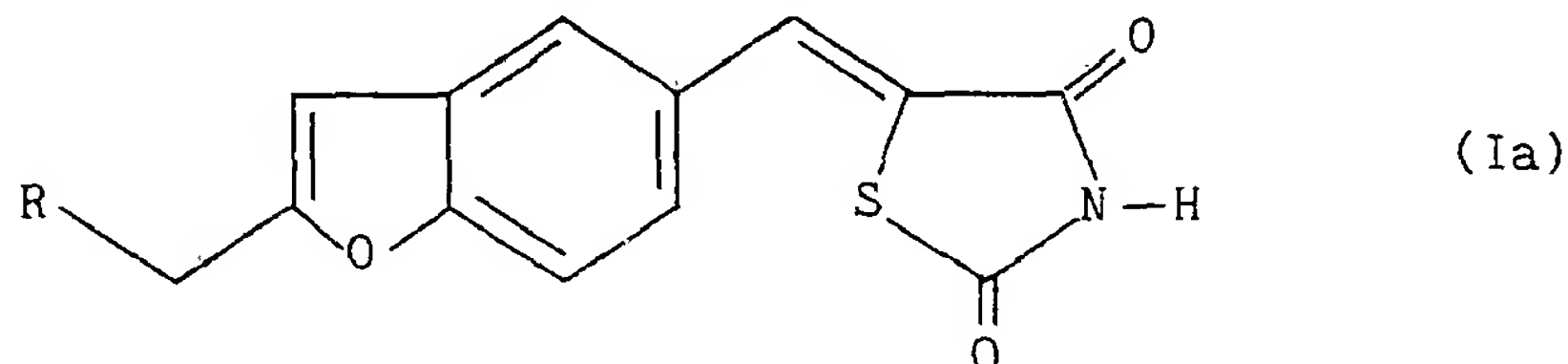
in which formula R is as described above, which is converted to a compound of formula (V) with cuprous cyanide:



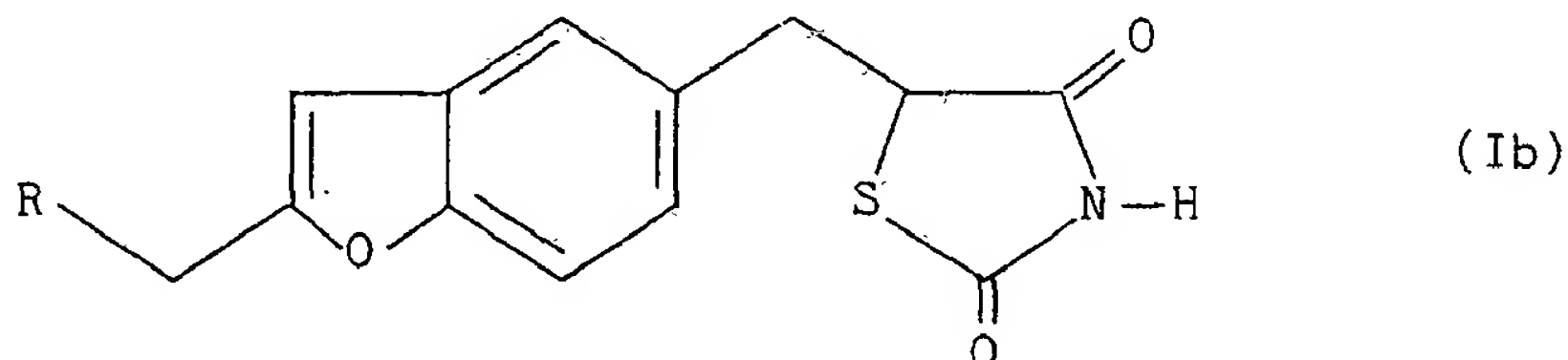
where R is as described above, to give, by reaction with an aluminum/nickel amalgam in the presence of acid such as, for example, trifluoroacetic acid, the compound of formula (VI):



in which R has the same meaning as above, which compound (VI) is condensed with 2,4-thiazolidinedione in the presence of a base such as piperidine so as to obtain the compound (Ia), a special case of the compounds of formula (I):



where R is as described above, which, on catalytic hydrogenation, yields the product (Ib), a special case of the compounds of the formula (I):



10 where R is as described above,
which compounds of formulae (Ia) and (Ib) are purified, where appropriate, according to a standard purification technique, and the isomers of which are separated, if so desired, by a
15 standard separation technique, and which are converted, if necessary, to their addition salts with a pharmaceutically acceptable acid.

20 5. A pharmaceutical composition containing as active principle at least one compound as claimed in any one of claims 1 to 3, alone or in combination with one or more pharmaceutically acceptable, non-toxic, inert vehicles.

25 6. The pharmaceutical composition as claimed in claim 5, containing at least one active principle as claimed in any one of claims 1 to 3, which is useful in the treatment of non-insulinopenic diabetes, associated with hypertension or otherwise.

DATED this 4th day of March 1993.
ADIR ET COMPAGNIE

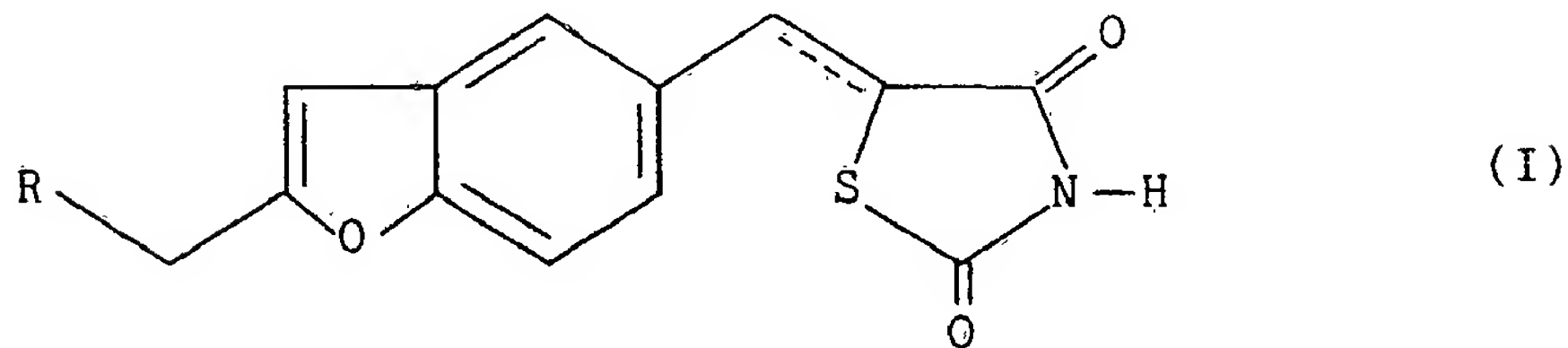
WATERMARK PATENT & TRADEMARK ATTORNEYS
"THE ATRIUM"
290 BURWOOD ROAD
HAWTHORN. VIC. 3122.

ABSTRACT

NEW 2,4-THIAZOLIDINEDIONE COMPOUNDS,
PROCESS FOR PREPARING THEM AND
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

ADIR ET COMPAGNIE
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Compounds of the formula (I):



in which:

- the broken line indicates the presence or absence of a double bond,
- R represents any one of the groups A or B as defined in the description.

Medicinal products.